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EXAMINER	
SAOUD, C	
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DATE MAILED: 04/02/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11/6/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 21-23, 25-27 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-20, 24, 28-30 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 21-23, 25-27 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Claims 29-30 have been cancelled, therefore, any rejections made on these claims are moot, and therefore, withdrawn. Claims 21-23 and 25-27 have been amended and are under consideration by the Examiner.

Response to Amendment

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The objection to the Specification and rejection of claims 21-23, 25-27, and 29-30 made under 35 U.S.C. § 112, first paragraph are moot upon amendments to the claims.

The rejection of claims 29-30 under 35 U.S.C. § 102(e) is moot upon cancellation of the claims.

Applicants' arguments filed 6 November 1995 in the amendment have been fully considered but they are not deemed to be persuasive with regard to the 103 rejection.

Claim Rejections - 35 USC § 103

As stated in the previous Office action, upon cancellation of language reciting "in a native conformation" from claims 21-23 and 25-27, an art rejection of these claims will now be made:

Claims 21-23 and 25-27 are rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO

163,529) either in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) essentially as applied to the claims in the prior Office action (paper #19).

As was interpreted by Applicants, the teachings of Markussen et al. is as follows: Markussen et al. ('212) discloses and claims insulin precursors of the form B(1-29)-X_n-Y-A(1-21). "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and "Y" is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. A preferred embodiment is B(1-29)-Ser-Lys-A(1-21). This precursor protein is a single peptide chain. This precursor is converted to human insulin by derivatization and treatment with trypsin. (See '212 at col. 2, line 65 through col. 3, line 46; Examples 11, 13, and 16; and claims.) Fusion proteins and their cleavage from the precursor are disclosed. (See col. 5, lines 11-20.) DNA sequences encoding the insulin precursor, expression vectors, transformed yeast cells, and recombinant methods of production in yeast (as well as E. coli holding plasmids encoding the desired insulin precursors) are also disclosed and claimed.

Applicants begin by arguing that "there would have been no suggestion in the applied prior art to try Applicants' invention nor would there have been any motivation to try their invention" (page 9 of response). However, Applicants' invention was already known because Grau ('332) specifically discusses the mono-Arg-insulin species of miniproinsulin and that it is exceptionally stable to further

tryptic degradation (col. 2, lines 10-12). Grau ('332) not only suggests the compound of the instant application, but provides motivation to obtain it because it is "exceptionally stable".

Applicants continue that "insulin precursors of both Markussen references do not render their mono-Arg-insulin obvious. Further, since the insulin claims relate to a process of using mono-Arg-insulin, the nonobviousness of the mono-Arg-insulin product itself is relevant to the nonobviousness of the process of using the mono-Arg-insulin. In re Pleudeman, 910 F.2d 823 (Fed. Cir. 1990)" (page 10 of response). Applicants state, "it is well established that disclosure of a generic formula does not necessarily render a species of the disclosed genus obvious" and "Markussen's disclosed generic formula does not necessarily render Applicants' species obvious, and the size of the genus should be considered in determining obviousness." Applicants go on to discuss the small odds of selecting their mono-Arg-insulin and that Applicants' mono-Arg-insulin compound is nonobvious (page 11 of response).

To answer these arguments, Applicants are correct in their assessment of Jones in that a genus does not ***necessarily*** render a species obvious. However, in this case, Applicants' mono-Arg-insulin was already known. Grau ('332) specifically discusses this species of miniproinsulin in that "it is surprising that the derivative insulin-Arg^{B31}-OH in crystalline form is exceptionally stable to further tryptic degradation" (col. 2, lines 10-12). Therefore, Applicants' species of mono-Arg-insulin was not only obvious, but also anticipated by the prior art. Grau teaches that this form of insulin

has the advantage of being stable and resisting further tryptic degradation. Therefore, one of ordinary skill in the art would have been motivated to use a precursor of insulin with the formula of Markussen et al. wherein X is Thr, n is 1, Y is Arg, and m is 1, in order to obtain mono-Arg-insulin of Grau. Grau ('332) provides the motivation to obtain mono-Arg-insulin because of its stability, thereby making obvious the species of X=Thr, n=1, Y=Arg, and m=1 in Markussens' generic formula. Therefore, the specific species was obvious, not because it is one a number of possible molecules that can be formed with the formula, but because Grau teaches that the product of mono-Arg-insulin is desirable and has the property of being stable and the use of Markussen et al.s' invention wherein the formula is X=Thr, n=1, Y=Arg, and m=1 would provide for mono-Arg-insulin, which is taught by Grau.

Applicants assert that one of ordinary skill in the art would have been dissuaded from methods that use a mono-Arg miniproinsulin. This argument is not deemed persuasive because the prior art teaches that mono-Arg-insulin is exceptionally stable, which would motivate the skilled artisan to use it. Applicants cite Thim et al. (PNAS 83: 6766-6770, 1986) as evidence that trypsin would not cleave a mini-proinsulin with an Arg-Arg or Lys-Arg bridging C chain. However, Markussen et al. teach that "arginine- and lysine-cleavage sites adjacent to the desired protein enables cleavage with trypsinlike proteases" (see U.S. Pat. No. 4,916,212, col. 4, lines 26-29). Applicants' arguments bridging pages 11 and 12 are not clear because Applicants' invention does not required cleavage of B and A chains linked by Arg-

Arg or Lys-Arg by trypsin alone, therefore the negative teaching of Thim et al. as to the necessity of another protease in addition to trypsin would not be applicable to the instant invention. The Arg linking the B and A chains is bound to Thr and Gly, respectively in the instant invention and therefore, this argument has no basis.

Applicants' final argument is that the method claims recite simultaneous trypsin and carboxypeptidase B incubation and that "simultaneous incubation is nowhere taught or suggested by the Markussen references, nor do the other references correct this deficiency." This is not true because Grau ('684) teaches using trypsin and carboxypeptidase B simultaneously to produce mature insulin from proinsulin. (See col. 5, lines 49-59.) It would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. first to Mono-Arg insulin and then to insulin. Grau ('332) teaches that Mono-Arg insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. One would have been motivated to use both trypsin and carboxypeptidase B in order to produce insulin from the precursor of Markussen et al. for treating diabetes.

Applicants argue that Markussen et al. ('332) would not be able to utilize both trypsin and carboxypeptidase B together. However, the instant rejection is not made over Markussen et al. ('332) and therefore, this argument is moot. Applicants state that the process of Markussen et al. ('529) cannot involve simultaneous trypsin and

carboxypeptidase B incubation because the precursors of this reference are missing Thr^{B30}. However, this is an obviousness rejection, and the method of Markussen et al. ('529), employing the species wherein X is Thr, n is 1, Y is Arg, and m is 1, would be cleaved by the combination of trypsin and carboxypeptidase B and result in the production of mono-Arg-insulin.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 4PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Garnette D. Draper, can be reached on (703) 308-4232. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.

CA

March 28, 1996

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800